UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/181,108	10/28/98	MILLER B	176/60440-(1

HM12/0717

PETER ROGALSKYJ
NIXON HARGRAVE DEVANS & DOYLE
CLINTON SQUARE
P O BOX 1051
ROCHESTER NY 14603

EXAMINER	
CELSA, B	
ART UNIT	**PAPER NUMBER**
1627	14

DATE MAILED: 07/17/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

file copy

Office Action Summary

Application No.	Applicant(s)
09/181,108	Miller et al.
Examiner	**Group Art Unit**
Bennett Celsa	1627

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

/

Disposition of Claims

☒ Claim(s) *1-40* is/are pending in the application.

Of the above, claim(s) *8, 9, and 11-40* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-7 and 10* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5,5,8,12*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

Status of the Claims

Claims 1-40 are currently pending.

Claims 1-7 and 10 are under consideration.

Claims 8-9 and 11-40 are withdrawn from consideration as being directed to a nonelected invention.

Election/Restriction

1. Applicant's election with traverse of Group I (claims 1-10) in Paper No. 10 is acknowledged. The traversal is on the ground(s) that Groups I and IV include the subject matter of claim 1 so they can not be separte and distinct. This is not found persuasive because reasons as to why and how Groups I-IV represent patentably distinct were provided in the office action in paper no. 9 on pages II-IV including compositional differences between Groups I and II; and the fact that separtely burdensome manual and/or computer searches are required with art-recognized divergence of subject matter (e.g. compostion requiring receptor v. librarary v. method of use v. Method of making which are drawn to different chemical compound structures, reagents and objectives etc.

The requirement is still deemed proper and is therefore made FINAL.

2. Applicant's election without traverse of the species of bis-N-[2-(2-aminomethyl)-1-methyl pyrrolidine]salicyladimanate Zinc II in Paper No. 13 which reads on claims 1-7 and 10 in response to the Supplemental Election of Species in paper no. 11 is gratefully acknowledged.

3. Claims 8-9 and 11-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-7 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The present claims are directed to combinatorial libraries which are broadly characterized as comprising a plurality of six different "complexes" .

The "complexes" are "formed of":

a. "at least two" "non-biopolymer ligands" (A^i) capableof reversibly binding a

b. "complexing agent" (Z). SEE application claims 1-5 and 10.

Application claim 6 selects at least one "A^i" to be a "DNA intercalator" OR a "major or minor groove DNA binder". However, in this regard the specification appears to refer to the claim 6 limitation elements as being a distinctly different moeity (e.g. a "recognition element" ????: see specification page 8).

Application claim 7 selects Z to be a "transition metal".

With the exception of claim 7 (e.g. transition metal) there is no claimed structure which corresponds to either the "complexing agent" OR "non-biopolymer ligands" which is necessary to define the overall structure.

The term "complexing agent" and "non-biopolymer ligands" are purely "functional" terms which do not represent an identifying characteristic as to correspond to any chemical compound structure since the metes and bounds of "complexing agent" and "non-biopolymer ligands" is totally unclear.

This is true since the term "complexing agent" is broad enough to read on anything that attaches (e.g. covalently, ionically or otherwise) to anything else. There is no core structure whatsoever that one could envision as being characteristic of a "complexing agent".

Similarly, the term "ligand" in its broadest sense is something (e.g. compound, element etc: including water) that attaches (e.g. covalently, ionically or otherwise) to anything else. There is no core structure whatsoever that one could envision as being characteristic of a "ligand"

Additionally, the claims are completely devoid of how and/or where the "complexing agent" attaches to the "non-biopolymer ligands" and/or "recognition element(s)" to formulate the ultimate chemical structure of the different "complexes" which consitute the library.

The specification description directed is directed to specific "complexing agent" and "non-biopolymer ligands" which clearly do not provide an adequate representation regarding the open ended claimed library compounds made by the presently claimed invention.

The unpredictability of ligand receptor binding is known in the art. . Additionally, the effects, a priori, of nonconservative substitutions which differ sterically and/or hydrophobically on substrate/ligand binding is unpredictable; for substrate/ligand binding is stereospecific for a compound (e.g. an organic compound or peptide/protein etc of the proper conformation ie. three dimensional structure). Additionally, changes in conformation resulting from different compound ligand structure (or ultimate complex structure) would be expected to differ in an unpredictable manner.

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

Although directed to DNA compounds, this holding would be deemed to be applicable to any compound; which requires a representative sample of compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the claimed generic(s).

In the present instance, the claimed invention contains no definite identifying characteristics regarding the individual "complex" components and their structural

interrelationship so as to demonstrate possession of the full scope of "complex libraries" presently claimed.

Additionally, the narrow scope of examples directed to specific complex library structures (e.g. see examples) is clearly not representative of the scope of combinatorial library compounds of the presently claimed invention..

6. Claims 1-7 and 10 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabled. The presently claimed invention::

a. Lacks essential subject matter (e.g. See *Ex parte Bhide* cited below); AND

b. Is not enabling for both making and use.

The unpredictability of ligand receptor binding is known in the art. . Additionally, the effects, a priori, of nonconservative substitutions which differ sterically and/or hydrophobically on substrate/ligand binding is unpredictable; for substrate/ligand binding is stereospecific for a compound (e.g. an organic compound or peptide/protein etc of the proper conformation ie. three dimensional structure). Additionally, changes in conformation resulting from different compound ligand structure (or ultimate complex structure) would be expected to differ in an unpredictable manner.

Accordingly, the material composition of the claimed complexes and ligands thereif which are critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

In this regard, it is noted that claims which lack critical or essential subject matter which is necessary to the practice of the invention, but is not included in the claim(s), including essential compound structure, . is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976); and *Ex Parte Bhide* (Bd Pat. App. & Int.) 42 USPQ2d 1441.

Turning to enablement is it noted that The term "complexing agent" and "non-biopolymer ligands" are purely "functional" terms which do not represent an identifying characteristic as to correspond to any chemical compound structure since the metes and bounds of "complexing agent" and "non-biopolymer ligands" is totally unclear.

This is true since the term "complexing agent" is broad enough to read on anything that attaches (e.g. covalently, ionically or otherwise) to anything else. There is no core structure whatsoever that one could envision as being characteristic of a "complexing agent".

Similarly, the term "ligand" in its broadest sense is something (e.g. compound, element etc: including water) that attaches (e.g. covalently, ionically or otherwise) to anything else. There is no core structure whatsoever that one could envision as being characteristic of a "ligand"

Additionally, the claims are completely devoid of how and/or where the "complexing agent" attaches to the "non-biopolymer ligands" and/or "recognition element(s)" to formulate the ultimate chemical structure of the different "complexes" which consitute the library.

The specification description directed is directed to specific "complexing agent" and "non-biopolymer ligands" which clearly do not provide an adequate representation regarding the open ended claimed library compounds made by the presently claimed invention.

As such, with respect to the claims, the specification fails to adequately provide guidance or examples of "how to make and use" all the molecules that would comprise the claimed complexes (e.g. ligands, complexing agents etc.) commensurate in scope with the claims in the absence of undue experimentation because the requisite chemical composition having the necessary structural (organic, inorganic, etc) and/or functional properties are not defined by what they are, but in fact by what they are not, which is insufficient to distinguish the complexes and ligands thereof in such a way that the testing of an inordinate number of compounds (known and unknown) could be circumvented.

Accordingly, applicant's claimed scope of compounds represents an invitation to experiment regarding possible drug candidate compound selected from among a pool of billions of possible peptides which are within the scope of applicant's generic.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-7 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claims 1-7 and 10 the metes and bounds of compounds (e.g. chemical structure) encompassed by the terms

- "complexing agent"
- "non-biopolymer ligand" and
- "recognition element" (e.g. see claim 6 and specification page 8)

All of the above terms are purely functional in nature which is not indicative of a particular chemical compound.

For example, is the term "complexing agent" a COMPOUND or a "COMPOSITION. If a composition what are the structures of the individual components? If a compound, what are the compound or compounds being "complexed" and what is the requisite structure of the "agent" required to perform such a function?

Similarly, the term "ligand" is totaly nondescript with regard to a structure which corresponds to the term ligand . The specification definition of a "non-biopolymer ligand" on page 6 is exemplary of this point: e.g. " those which reversibly bind to the complexing agent" . The

definition is totally nondescript since "the complexing agent" is indefinite; the means of binding (e.g. covalent, non-covalent or otherwise"; and how it "binds" is indefinite. Similarly, the term "non-biopolymer" is confusing since the distinction between biological and non-biological polymers is not understood. Is this a synthetic distinction; e.g. non-biological polymers are not made by living organisms?

B. Claims 1-7 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. It is totally unclear as to how the different "complex" components (e.g. ligands and/or "recognition elements" (with or without linkers and "complexing agents") interelate or come together chemically to make the final complexes which comprise the library. See MPEP § 2172.01.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-7 and 10 are rejected under 35 U.S.C. 102(a) as being anticipated, or in the alternative as obvious over Klekota et al. Tetrahedron Letters Vol. 38, No. 50 (12/15/97).

The Klekotat et al. reference discloses a combinatorial library of 36 uniquie bis (salicyclaldimainoto) zinc complexes (including the elected species) at least one species of which binds oligo dA (e.g. affinity chromatography) clearly anticipating claims 1-7. The extension of the above example either to other transition metals (e.g. nickel etc) would immediately envisage the generation of libraries of higher number (e.g. at least 100 complexes: e.g. claim 10) or in the

alterantive the making of larger libraries would be obvious to one of ordinary skill in the art in the nature of scaling up to find additional "novel DNA binding compound" for prospective diagnostic and/or harmacological use (e.g. transcription regulators; probes etc)

12. Claims 1-6 and 10 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Benner, U.S. Pat. No. 5,958,702 (9/99: filed 2/95).

Benner discloses "receptor-assisted combinatorial chemistry" comprising the complexing of atoms, groups of atoms or ions on a receptor (e.g. the complexing agent) with two (e.g. A-x-yB: see col. 5-6) or "more than two member ligands of a library (e.g. via disulfide bonds: e.g. see Example 8; patent claims 1-5) and thus generate a combinatorial library which would be expected to comprise "a plurality of at least six different complexes within the scope of the presently claimed invention. The reference ligands are within the scope of the presently claimed ligands (e.g. non-biopolymers) and additionally comprise ligands which are "recognition elements" that are capable of being classed as "DNA intercalators" or "major or minor groove DNA binders" within the open ended specification definition of these terms in the specification (e.g. see specification pages 7-10 which encompass "hydroxy"; "alkoxy" or "amine" groups which are within the scope of the presently claimed invention (e.g. S-C(OH) as hydroxy: Example 8 general formula comprising an alkoxy (OR) group. Again the Examiner lacks the facilities to determine whether the reference ligands or covalent bonds comprising the ligand are capable of functioning under the overly broad specificaition definition for "recognition elements".

13. Claims 1-7 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Blackborow et al., J. Chem. Res (S) Jan. 1978 page 119..

Blackborow et al. disclose a combinatorial library of a "plurality of at least six different complexes" which comprises a complex having a complexing agent (e.g a transition metal: zinc) and a monomers (which would include D/L optimers and thus are distinctly different ligands), dimers (of two distinctly different structure) and/or trimers in which the ligands are salicyclaldiminatozine derivatives which clearly anticipate claims 1-5 and 7. The salicyclaldiminatozine derivative ligands are "recognition elements" that are capable of being classed as "DNA intercalators" or "major or minor groove DNA binders" within the open ended specification definition of these terms in the specification (e.g. see specification pages 7-10 which encompass "hydroxy"; "alkoxy" or "amine" groups which are within the scope of the presently claimed invention) with these ligands being either phenyl substituted derivative which further cormprise an amine moeity. The Examiner lacks the facilities to determine whether the reference ligands are capable of functioning under the overly broad specificaition definition for "recognition elements".

14. Claims 1-7 and 10 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Jacobsen et al. WO 98/12156 (3/98)..

Jacobsen et al. disclose a combinatorial approach for generating novel coordination complex mixtures of "at least 6" (e.g. see page 6, lines 5-10) by coordinating to a transition metal (e.g. including zinc: see e.g.. Page 6, lines 17-26) and ligands (e.g. non-biopolymer: see e.g. pages 25-31) to form bidentate, tridentate, tetradentate or even higher order metal chelating ligands (e.g. see page 6, lines 7-10; and abstract). Accordingly, the reference would anticipate the generic concept of present claims 1-5, 7 and 10.

Additionally, a large number of the reference ligands (e.g. see pages 25-31) comprise substituted and unsubstituted aryl and heterocyclic moietes which would constitute "recognition elements" that are capable of being classed as "DNA intercalators" or "major or minor groove DNA binders" within the open ended specification definition of these terms in the specification (e.g. see specification pages 7-10 which encompass aryl and heterocycles as well as "hydroxy"; "alkoxy" or "amine" groups which are within the scope of the presently claimed invention) with these ligands being either phenyl substituted derivative which further comprise an amine moeity. The Examiner lacks the facilities to determine whether the reference ligands are capable of functioning under the overly broad specificaition definition for "recognition elements". Alternatively , the selection of such an intercalating ligand would be obvious to one of ordinary skill in the art. Reference claims 29-30 and Fig. 1-11 disclose specific reference library combinations which anticipate the presently claimed invention.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat (art unit 1627), can be reached at (703)308-0570.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1627)

July 13, 2000

BENNETT CELSA
PRIMARY EXAMINER